

REMARKS

Applicant respectfully thanks the Examiner for considering the present amendment and remarks. It is acknowledged that the Examiner has stated that claims 36-41 would be allowable if rewritten in independent form. Claims 36-41 have been cancelled and rewritten in independent form and are now claims 64 - 69.

Reconsideration of this application is requested. Claims 1-45 were pending in the case. However, the claims have been amended as noted herein. Claims 46 - 73 are now pending in the case.

Claims 46 - 63 correspond to previously amended claims 4, 7, 8 and 10-24.

Claims 64 -69 were rewritten in independent form as noted-above and correspond to claims 36-41 that were cancelled in the application.

Claims 70 and 71 are also dependent from claim 64.

Support for claim 70 can be found at page 17, Table 2.

Support for claims 71 - 73 can be found at page 25, line 32 and page 26, line 1.

Applicant has amended the claims to be directed to biocompatible hemoglobin capable of oxygen transport (see page 7, lines 5-6 of the application) chromanol antioxidant conjugates and reserves the right to pursue any other aspects of the invention in a further continuation or continuation-in-part application. No amendment is to be construed as a basis to deny any right to invoke the doctrine of equivalents in construction of any allowed claims or an admission of any sort.

The Figures have been amended in response to the Draftspersons objection under 37 CFR 1.84 or 1.152.

I. **RESPONSE TO AMENDMENT**

With regard to the Examiner's statement that P50 of the conjugate has no support in the disclosure, Applicant has included claims 71 -73 that refers to the human hemoglobin conjugated with Trolox having a P50 of 41, 40 and 16 mm Hg. Support can be found in the disclosure at page 25, line 32 to page 26, line 1.

II. **DRAWINGS**

We make note of the Examiner's rejections of the drawings and his statement that formal drawings will be required when the application is allowed. Applicant herein encloses amended drawings.

III. **CLAIM REJECTIONS - 35 U.S.C § 112**

With regard to the Examiner's statement that it is not clear what is meant by "the P50 of the conjugate is 40". Applicant respectfully refers the Examiner to page 25, line 32 to page 26, line 1. It is submitted that a person skilled in the art would understand what is meant by the "p50 of the conjugate". Further claims 71 - 73 now refer to "a" p50 to correct the antecedent issue.

The Examiner rejected claims 11, 12 and 23 on the basis of typographical errors. Applicant has attended to the typographical errors in new claims 50, 51 and 62.

IV **CLAIM REJECTIONS 35 USC § 102**

The Examiner rejected claims 1 - 3, 13-15 and 20 as being anticipated by Kluger (WO 97/00236). It is submitted that this rejection is no longer applicable in light of the new claims that are now directed to chromanol conjugates. The Examiner rejected the claims on the basis that Kluger discloses hemoglobin epinephrine and norepinephrine conjugates. It should be noted that these conjugates are described in Kluger as hormones and not antioxidants. In any event, epinephrine and norepinephrine are not chromanols.

The Examiner rejected claim 45 as being anticipated by Levy et al. (US 5780060). Claim 45 has been cancelled without prejudice to pursue this claim in a later continuation, continuation-in-part or divisional application.

V. CLAIM REJECTIONS 35 USC § 103

The Examiner rejected claims 4, 7-8, 10 -12, 16-19, 21-24 and 42-44 [Now corresponding to new claims 46-63] as being obvious in light of Hsia (US 5789376) and Beach et al. (Archives of Biochemistry and Biophysics 1992 abstract, 297 (2), 258-64). Applicant respectfully traverses this rejection.

It is noted that the Examiner has stated that the claims directed to the hemoglobin-Trolox composition or conjugate are allowable on the basis of the unexpected synergistic effect. Applicant respectfully submits that the same argument can be extended to the hemoglobin conjugated to any one of the antioxidant chromanol within the Trolox family. As such, it is respectfully submitted that the claims do not need to be unnecessarily restricted Hemoglobin-Trolox compounds *per se* and that the experiments and description adequately enable the full range of said family of conjugates. It is submitted that the application sufficiently teaches a person of ordinary skill in the art to practice the invention without undue experimentation and a reasonable expectation of success. Once the present inventors have shown the unexpected enhanced effect of the Hb-Trolox conjugates as described in the present application, a person of ordinary skill in the art would reasonably expect the same surprising results with other chromanols, which have shown to be a class of superior antioxidants. None of the prior art teach or predict the surprising enhanced antioxidant effects of Hb-chomanol compounds over chromanols alone.

Further, it is respectfully submitted that one of ordinary skill could not have combined Hsia with Beech et al. to get a conjugate that both transports oxygen and that can ameliorate antioxidant activity of a bound chromanol antioxidant. Beech describes the use of chromanols as

having superior antioxidant activity, but does not teach or suggest conjugating the chromanols to other macromolecules or to hemoglobin. Nor does Beech et al. anywhere suggest the surprising enhanced antioxidant properties of chromanol conjugates. It is respectfully submitted that there is no motivation in Beech et al. to produce a chromanol conjugate as described in the present invention.

Hsia described hemoglobin-nitroxide conjugates. Hsia specifically restricts the description to the use of nitroxides no other antioxidant conjugates are suggested or recommended. Chromanols are not suggested. Hsia specifically selects nitroxides as it mimics the natural enzyme, superoxide dismutase (SOD) present in red blood cells (column 5, line 30) and further because nitroxides were known vasorelaxants. Nitric oxide had been identified as the endothelium-derived relaxing factor (EDRF) (column 4, lines 16 - 19). Hsia describes two effects of nitric oxide, its reaction with the superoxide anion; and the extravasation and the binding with hemoglobin (column 4, lines 40 - 41). Column 7, lines 50-61 and column 9, line 48 to column 11, line 22 describe the preferred forms of nitroxide. When describing other applications of the technology at column 14, lines 45-53, application of the technology with other antioxidants are not mentioned. It is respectfully submitted that there would be no motivation from Hsai to attempt to use an antioxidant other than a nitroxide.

As such it is respectfully submitted that it would not have been obvious to combine the teachings of Hsia and Beech to make a hemoglobin-chromanol antioxidant to obtain the present invention.

ADAMSON et al
Serial No. 09/926,167

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.
Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact Anita Nador by telephone at (416) 957-1684 at his convenience.

Respectfully submitted,

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